

Following the Track to an Unexpected Diagnosis: Phaeohyphomycosis

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Contributors' Statements

Mr. Mohammed conceptualized the report, reviewed and revised the manuscript.

Dr. Rahnema-Moghadam conceptualized the report, obtained the photos, reviewed and revised the manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Presentation

A 77-year-old man with a history of diffuse large cell B-cell lymphoma (DLBCL) and 7 cycles of chemotherapy (CHOP) plus rituximab presented to the dermatology clinic with a nodule overlying the left 5th dorsal metacarpal phalangeal joint of 2-3 months duration. The nodule was pink and rubbery, fixed in place with overlying scale and crusting. There was initial concern for a skin cancer given his history of actinic keratoses and 4 prior skin cancers in the past. He had intermittent sweating and weight loss that occurred during his chemotherapy cycles, but not otherwise. During one of his hospitalizations he had developed atrial fibrillation and was prescribed amiodarone. On review of symptoms, he mentioned having an occasional headache and sinusitis like symptoms. He did not have any neck stiffness, paralysis, paresthesias, diplopia, nor history of seizures.

Assessment

On exam, he had a scaly rubbery pink-brown nodule to the left dorsal hand with some heme crust at the center of the lesion—this lesion was non-tender (see Figure 1). At the left forearm there were a series of 3 rubbery pink-brown non-crustated papules, linearly arranged (see Figure 2). These were non-tender as well. When questioned about these papules, he noted that they occurred approximately 18 months ago after he was receiving intravenous contrast for a CT scan being done for the purpose of staging his lymphoma. A few days after the intravenous contrast was given, he participated in a home renovation that resulted in exposure to dusty conditions during the demolition phase. The lesions were non-tender to palpation and he regarded them as scars. He had neither epitrochlear nor axillary lymphadenopathy on his left side.

Given the uncertain differential diagnosis of the lesion on left dorsal hand and the curious linear arrangement of the forearm papules, a biopsy of each lesion was performed to evaluate for either a cutaneous malignancy (such as a squamous cell carcinoma) or an infectious etiology occurring in a sporotrichoid distribution, such as sporotrichosis, mycobacterial infection, other deep fungal infections including histoplasmosis and blastomycosis. Iododerma given the history of IV contrast was also considered.

The biopsy of both locations showed pseudoepitheliomatous hyperplasia with neutrophilic and granulomatous inflammation. Closer examination demonstrated pigmented hyphae in both the hand and forearm specimens (Figure 3 and 4). Skin tissue was cultured, and *Exophiala jeanselmei* was found.

Diagnosis

The patient was diagnosed with phaeohyphomycosis. Phaeohyphomycosis is caused by dematiaceous fungi from genera such as *Exophiala*, *Cladosporium*, *Phialophora* and *Wangiella*, which live worldwide in soil, trees, and decaying vegetation (1). Infection with such organisms can usually be traced to inoculation, from a source as simple as a splinter. Most infected patients had a history of working outdoors with light clothing (2) (3) (4) (5). Skin manifestations, including rash and ulcers, are commonly seen in patients, along with fever (6). Diagnosis of phaeohyphomycosis caused by *E. jeanselmei* involves both the presence of positive cultures and histopathologic evidence. Typical changes involve a granulomatous tissue response with infiltration of leukocytes and occasionally microabscess formation.

Microscopically, *Exophiala* initially appears as budding yeast-like cells that often form long chains. As they mature, septate hyphae, brown to black in color, develop that give rise to numerous tubular cells called annelides. These annelides usually narrow out and form elongated tips, which help to distinguish *Exophiala* from other dematiaceous fungi. (7) (8). Subcutaneous phaeohyphomycosis can occur in both immunocompetent and immunosuppressed patients (including solid organ transplant recipients and those being treated with corticosteroid); immunosuppression poses a greater risk of treatment failure and subsequent dissemination of the infection (9). Because phaeohyphomycosis often disseminates to many organs, cardiac and cerebral tissue can be involved, resulting in high mortality (case series report 80%) particularly if the central nervous system is affected (10). While there is no standard workup for phaeohyphomycosis infection, if the central nervous system is evaluated, MRI is the imaging modality of choice; MRI with diffuse weighted imaging and MR perfusion studies may even be useful in differentiating fungal central nervous system infections from pyogenic or neoplastic causes (11).

Management

For invasive and disseminated disease due to phaeohyphomycosis, surgical excision, if possible, should generally be combined with antifungal therapy. Itraconazole at doses of 400 mg/day or higher for at least 6 months is commonly used in treating this group of infections. Case reports have also demonstrated success with itraconazole and terbinafine, or voriconazole and terbinafine (12). For central nervous system disease, posaconazole has been effective, as have combinations of amphotericin B, flucytosine, and itraconazole. Complete excision of primary brain lesions may be prudent (10). In widely disseminated disease, debulking of skin may be of some value (6).

Our patient may have had an inoculation after developing a wound from the IV contrast extravasation and participating in the renovation of a dusty building. Due to a potential interaction with azole antifungal (itraconazole, voriconazole) and the patient's amiodarone, oral terbinafine 250 mg daily was used. After 2 weeks, on follow-up, however, the patient noted that the lesions had increased in size, had become tender, and he felt the treatment was failing. Given his continued headaches and sinusitis, he received an MRI of the brain with contrast, which did not show central nervous system involvement.

With the progression of the lesions, terbinafine and amiodarone were discontinued, and the patient was started on voriconazole 200 mg twice a day. After 6 weeks of therapy, the pain associated with the lesions lessened and the lesions flattened. He continued voriconazole for a full 12 week course, with only the side effect of mild vision blurring. He has been followed clinically for the past year without evidence of recurrence.

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Figure Legends

Figure 1: Crusted nodule with ulceration

Figure 2: Lesions on the hand and the forearm

Figure 3: 60X magnification of H/E of hand biopsy, granulomatous and suppurative inflammation and subtle pigmented hyphae (arrows).

Figure 4: PAS staining of hand biopsy (60X magnification) showing pigmented hyphae.



Figure 1



Figure 2

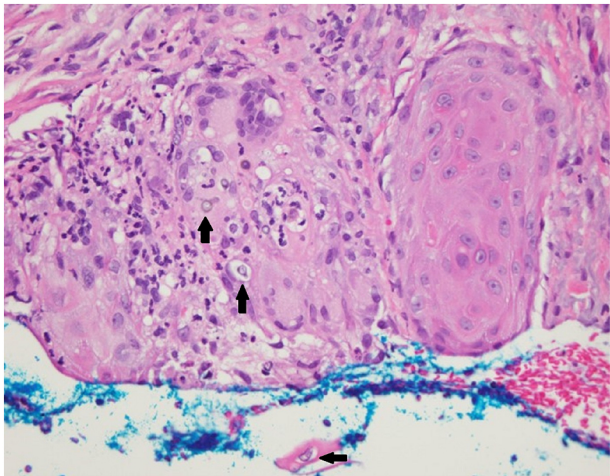


Figure 3

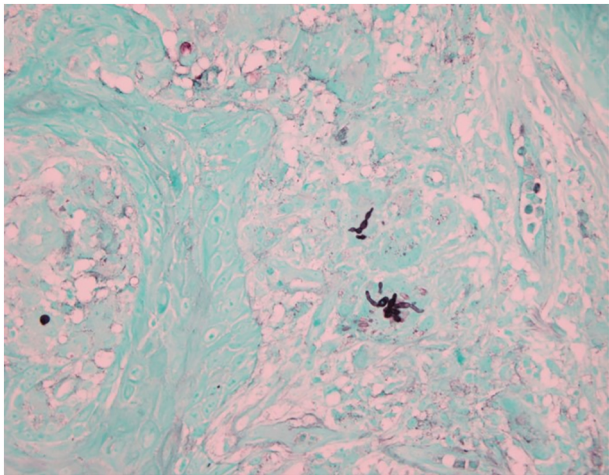


Figure 4